REMARKS

Claims 1-21 are currently pending in the application. Claims 2-3, and 7-21 are withdrawn. Claims 1 and 6 are proposed to be amended. New claims 22 and 23 are proposed herein. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Claim Amendment

Claim 6 as pending recites "under conditions sufficient for the covalent joining to form a ligated circular vector...." Applicants propose herein to amend this language to recite instead "under conditions sufficient for the covalent joining of said insert to said vector to form a ligated circular vector...." The amendment is intended to make the claim more grammatically correct. The amendment adds no new matter.

New Claims

New claim 22, dependent from existing claim 5, and new claim 23, dependent from new claim 22 are added herein to further describe embodiments of the claimed invention. The new claims, which recite *in vivo* site-specific recombination (claim 22) and the use of host cells expressing Cre recombinase for *in vivo* site-specific recombination (claim 23) are believed to fall squarely within the scope of elected Group I, because Group I claim 5 originally recited *in vivo* site-specific recombination as one method of joining the free ends of the vector arms. Cre-LoxP recombination is described in the specification at, for example, page 17, line 21 to page 19, line 2. *In vivo* site-specific recombination to join the free ends of the ligated molecule is also described at page 21, lines 8-11 and in Example 7, at page 31.

The new claims do not raise new issues requiring a new search because the new claims are narrower than claim 5, and a proper search of the limitations of claim 5 should have revealed relevant art relating to *in vivo* site-specific recombination, including site-specific *in vivo*

recombination via Cre-LoxP. Entry and consideration of the new claims is respectfully requested.

Rejection of Claims 1 and 4-6 Under 35 U.S.C. §103(a)

Claims 1 and 4-6 remain rejected under 35 U.S.C. §103(a) as obvious over the teachings of Shuman (U.S. Pat. No. 5,766,891) in view of Heyman et al. (Genome Research, 9:383-392, 1999), Pan et al. (J. Biol. Chem. 225: 890-901, 1993) and in view of Sambrook et al. (Molecular Cloning pp13-15, 1982). The Office Action states:

> Applicant should note that claims under examination are to be given their broadest reasonable interpretation. (Citation omitted) Given this tenet of patent examination, the cited art does indeed meet the limitations of the claims. The vectors of both Shuman and Heyman et al. indeed disclose topoisomerase bound at one end of a flanking molecule. The vectors of both references comprise two double stranded nucleic acid molecules, *i.e.*, one strand, in fact, flanks the other. The vectors of both references also show that the one end of each flanking nucleic acid molecule comprises a topoisomerase site which binds the topoisomerase molecule and therefore meets the limitation of the claims wherein "one end only of each of said first and second flanking molecules comprises a covalently bound topoisomerase polypeptide. See Shuman, figure 5 and Heyman et al. figure one. Therefore the present claims stand rejected under the cited prior art."

Applicants respectfully disagree.

The specification states that "'Nucleic acid molecule' refers to a double-stranded nucleic acid, unless otherwise specified" (see page 6, lines 19-20). Thus, a "nucleic acid molecule" in the context of the claimed invention is a *double stranded* nucleic acid molecule, not two single stranded molecules. As the term is used in the instant claims, then, a nucleic acid molecule comprising covalently bound topoisomerase on one end only is *not* a single stranded nucleic acid molecule with topoisomerase on one end, as suggested in the Office Action. The Office Action acknowledges that both Shuman and Heyman et al. teach double stranded nucleic acid molecules, but those double stranded nucleic acid molecules have topoisomerase on *both* ends,

not one end only. In view of this, neither Heyman et al. nor Shuman satisfies the limitations of the claims.

While it is believed that it is clear from the definition alone that "nucleic acid molecules" of the claims are double stranded, Applicants propose to amend claims 1 and 6 to recite double stranded nucleic acid in order to leave no doubt. In view of this, Applicants submit that neither Heyman et al., nor Shuman satisfies the requirement of covalently bound topoisomerase "at one end only" in each of the independent claims. Further, the Pan et al. and Sambrook et al. references do not remedy this deficiency. In view of this, no combination of Heyman et al. Shuman, Pan et al. and Sambrook et al. can provide all elements of the claims as proposed to be amended. Reconsideration and withdrawal of the §103 rejection is respectfully requested.

In view of the foregoing, Applicants submit that all issues raised in the Final Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Respectfully submitted,

Mark J. FitzGerald
Reg. No. 45,928 for
Kathleen M. Williams

Date: February 28, 2006

Name: Kathleen M. Williams
Registration No.: 34,380
Customer No.: 27495
Edwards Angell Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel. (617) 239-0100